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ORIGINAL ARTICLE

Preparation, characterization, and catalytic application of metallic nanocrystalline $MgAl_2O_4$ in the synthesis of 3-hydroxy-3-indolyl-indolin-2-ones, symmetrical and unsymmetrical 3,3′-bis(indolyl) indolin-2-ones, and 3,3′-bis(indolyl)methanes

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KEYWORDS

$MgAl_2O_4$;
Oxindoles;
Nanocatalyst;
Multi-component reaction (MCR)

Abstract Nanocrystalline $MgAl_2O_4$ has been synthesized via co-precipitation method and characterized by Fourier transform infrared spectroscopy (FT-IR), energy-dispersive X-ray spectroscopy (EDX), scanning electron microscopy (SEM), and X-ray diffraction (XRD) techniques. The synthesized nanocatalyst has been utilized for the one-pot condensation of indoles and isatins to prepare 3-hydroxy-3-indolyl-indolin-2-ones and symmetrical and unsymmetrical 3,3′-bis(indolyl)-indolin-2-ones. The one-pot pseudo three-component condensation of indoles and various aldehydes has also been examined to afford 3,3′-bis(indolyl)methanes. Short reaction times, reusability and recovery of the nanocatalyst, in addition to solvent-free reaction media are some advantages of this eco-friendly procedure.

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1. Introduction

Magnesium aluminate spinel, $MgAl_2O_4$, possesses industrial applications in sensors, nuclear techniques, refractory materials, dentistry, and transparent ceramics (Amini et al., 2015), because of its unique features such as high melting temperature (2135 °C), chemical inertness, good thermal shock resistance, and high mechanical strength (Navaei Alvar and Rezaei, 2009). It has also demonstrated catalytic activity (Zarnegar et al., 2015; Safari et al., 2013; Mosayebi et al., 2012). Several synthesis methods such as precipitation route (Li et al., 2001), sol–gel methods (Debsikdar, 1985), the citrate–nitrate route (Saberi et al., 2008), and microwave assisted combustion route

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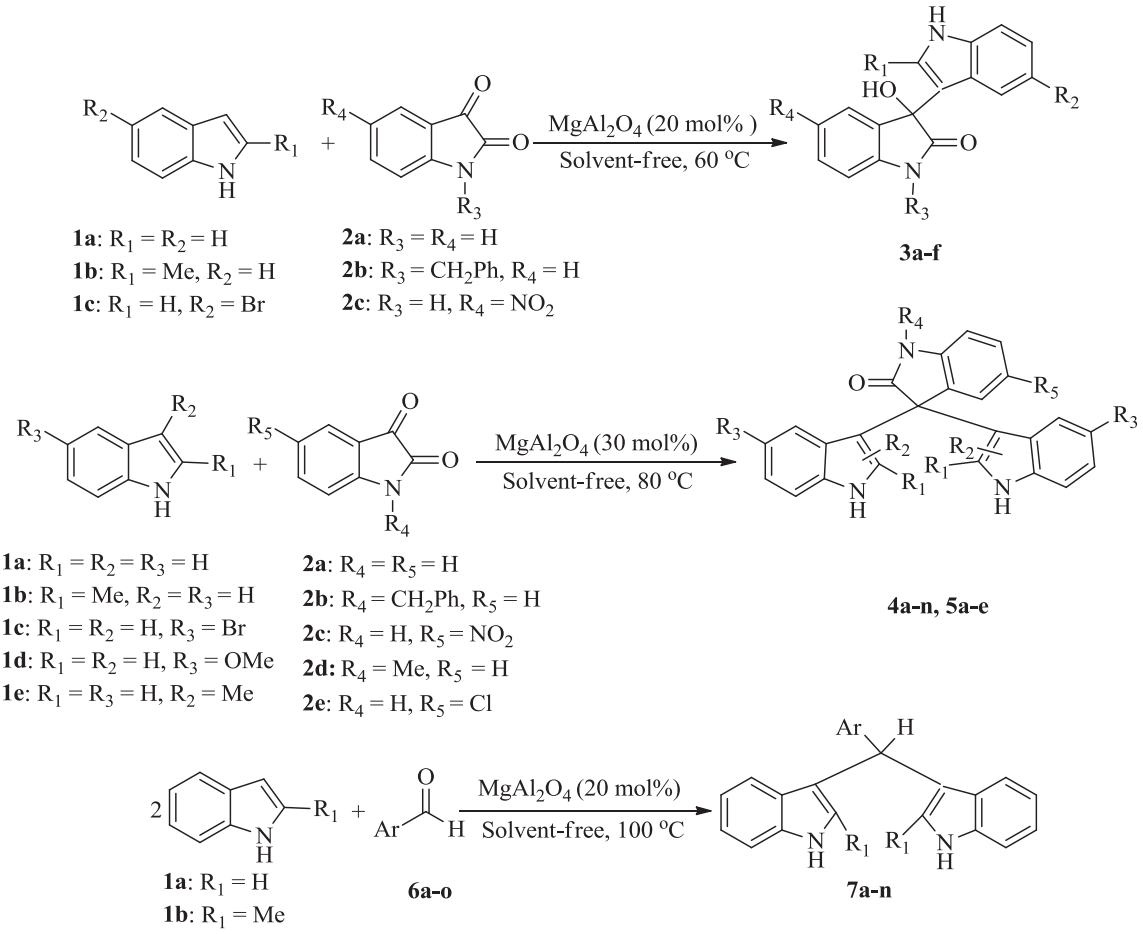


Scheme 1 Synthesis of 3-hydroxy-3-indolyl-indolin-2-ones **3a-f**, symmetrical **4a-n** and unsymmetrical 3,3′-bis(indolyl)indolin-2-ones **5a-e**, and 3,3′-bis(indolyl)methanes **7a-n**.

(Ganesh et al., 2005) have been used to synthesize fine nanocrystalline magnesium aluminate. Recently, nanocrystalline $MgAl_2O_4$ spinel powders are also prepared by co-precipitation method using CTAB as surfactant (Navaei Alvar et al., 2010). Because of wide-spread application of $MgAl_2O_4$, efforts to develop modified preparation methods that grow the properties such as high surface area, small crystallite size, and more active sites are still in demand.

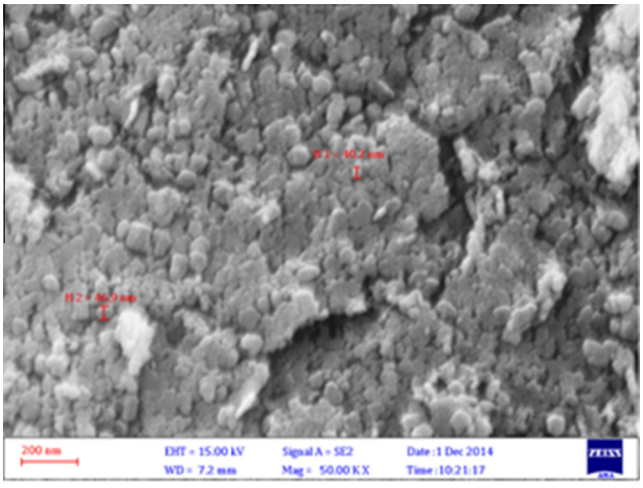
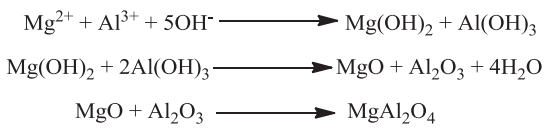


Figure 1 SEM image of $MgAl_2O_4$ nanoparticles.

Indole is a prevalent heterocyclic nucleus existing in many natural products possessing diverse physiological activities (Sundberg et al., 1992). In a large number of synthetic indole-based organics, which contain isatin, the indolin-2-one (oxindole) moiety has been observed. A great class of these *N*-containing heterocylces are 3,3′-bis(indolyl)i ndolin-2-ones which are fundamental motifs in the domain of drugs and biologically active compounds such as anti-proliferatives, antibacterials, anti-protozoals and anti-inflammatory agents (Joshi et al., 1984). They have also been used as laxatives (Garrido et al., 2004). 3-Hydroxy-3-indolyl-indolin-2-ones are another indole-based scaffolds with a broad spectrum of biological activities including anti-viral, antitubercular, anti-angiogenic, anti-fungal, anticonvulsant, and new targets for cancer chemotherapy (Galliford and Scheidt, 2007). Several pharmacologically active alkaloids such as Maremycin A and B, Flustramnol, Arundaphine, and several others contain 3-hydroxyoxindole moiety (Prathima et al., 2014). 3,3′-Bis(indolyl)methanes (di(indolyl) alkanes) are another category of spiro C-3 indolic compounds. Although they have been found in a number of sources, one of the earlier interesting discoveries was the beneficial metabolism of Strone promoted by Vibrindole A, which isolates from cruciferous plants such as



Scheme 2 Equative preparation of $MgAl_2O_4$.

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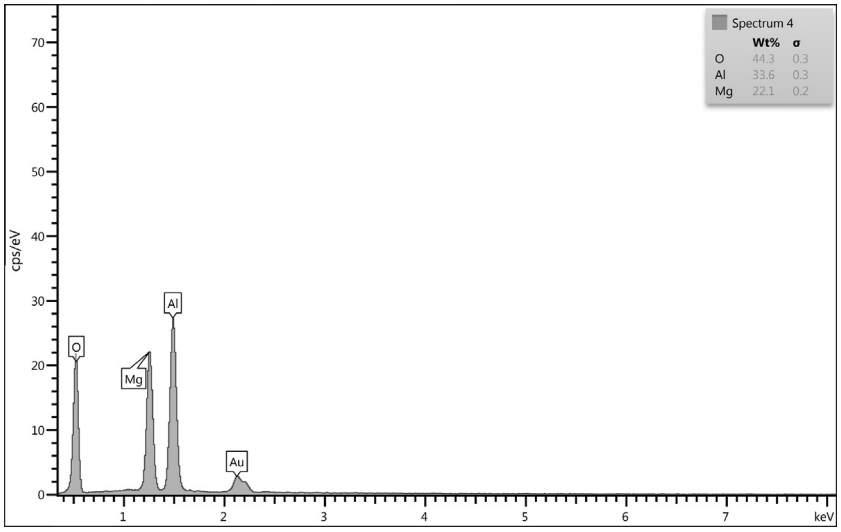

Figure 2 EDX pattern of nanocrystalline $MgAl_2O_4$.

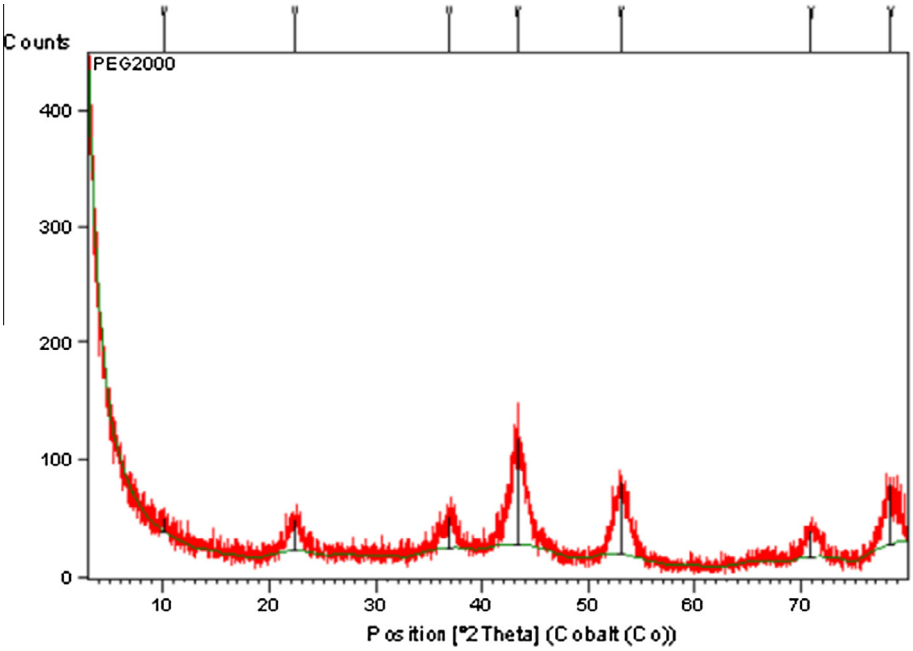

Figure 3 XRD pattern of the synthesized $MgAl_2O_4$.

broccoli (Osawa and Namiki, 1983). They also possess a wide range of biological and pharmacological activities such as anti-tumor, HIV-1 integrase inhibitor, and aromatase inhibitor for breast cancer (Swetha et al., 2015). Some of them showed chemotropic effects in the treatment of fibromyalgia, chronic fatigue, and irritable bowel syndrome (Kamble et al., 2007). Although many methods have been reported for the synthesis of these valuable compounds (Rad-Moghadam et al., 2010; Shanthi et al., 2009; Kumar et al., 2015; Alimohammadi et al., 2008; Nikpassand et al., 2010; Sharma and Sharma, 2010; Sarrafi et al., 2012; Hojati et al., 2013; Yang et al., 2011; Pal, 2013; Tayebee et al., 2011; Li et al., 2014), efforts toward the synthesis of these pharmacologically and industrially active frameworks are still interesting for many research laboratories.

In continuation of our research on indole heterocycles and nanocatalysts (Haghighi and Nikoofar, 2014; Mohammadpoor-Baltork et al., 2006; Ghanbari and Nikoofar, 2014), in current study, we introduced nano-$MgAl_2O_4$ as a novel effective and reusable catalyst for the synthesis of 3-hydroxy-3-indolyl-indolin-2-ones, symmetrical and unsymmetrical 3,3′-bis(indolyl)indolin-2-ones, and 3,3′-bis(indolyl)methanes under solvent-free and mild conditions (Scheme 1).

To the best of our knowledge, this is a novel modified preparation, and characterization of nanocrystalline $MgAl_2O_4$ and its application in the synthesis of spiro-indoles compounds.

2. Experimental

2.1. General

All chemicals were purchased from Merck, Aldrich and Alfa Aesar and were used without further purification. *N*-Benzylisatin is synthesized from isatin according to the

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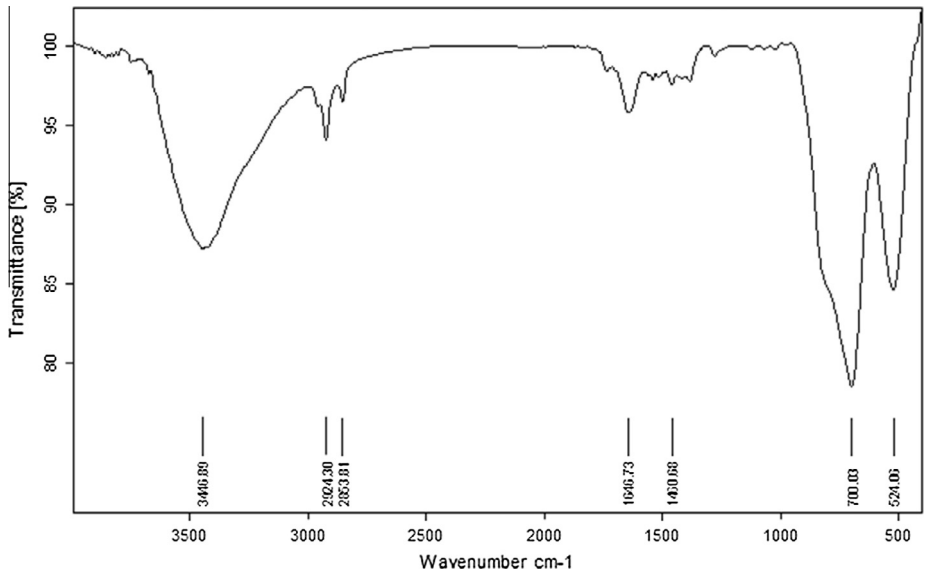
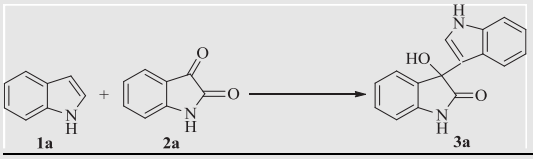


Figure 4 FT-IR spectrum of $MgAl_2O_4$.

reported procedure (Azizian et al., 2003). IR spectra were recorded from KBr disk using FT-IR Bruker Tensor 27 instrument. Melting points were determined on a Shimadzu DSC-50 thermal analyzer and are uncorrected. ^{1}H NMR spectra were recorded with a Bruker drx (400 MHz) machine. Elemental analyses were determined using a Thermo-Finnigan Flash EA 1112 Series. Progress of the reaction was monitored by thin layer chromatography (TLC) techniques using commercial available silica gel sheets. Preparative layer chromatography (PLC) carried out on 20 × 20 cm^2 plates, coated with a 1 mm layer of Merck silica gel PF_{254}, prepared by applying the silica as slurry and drying in air. The scanning electron microscope (SEM, model ∑-IJMA) was used to characterize the nano structures. The products were characterized by comparison of their melting points and also spectroscopic data (FT-IR, ^{1}H NMR) with those of the authentic samples in literature. An ultrasound bath (Wise Clean, Korea) has been used for sonication. The XRD pattern was done by an X-ray diffractometer, Philips, with Cu Kα1 radiation, cobalt anode with wavelength 1.7889 Å, 40 kV, 40 mA. The centrifuge apparatus was a RST16 full digital model with rpm 300 cycle/min.

Table 1 Optimization of the one-pot condensation of indole (**1a**) and isatin (**2a**) under various conditions.[a]



Entry	Solvent	Temperature (°C)	Catalyst (mol%)	Time (min)	Yield (%)[b]
1	H_2O	r.t.	20	205	51
2	H_2O	Reflux	20	150	72
3	CH_3CN	r.t.	20	60	53
4	CH_3CN	Reflux	20	65	45
5	EtOH	r.t.	20	160	67
6	EtOH	Reflux	20	20	52
7	–	r.t.	20	65	65
8	–	40	20	30	81
9	–	60	20	20	82
10	–	80	20	20	82
11	–	60	10	40	75
12	–	60	25	20	83

[a] Reaction conditions: indole (1 mmol), isatin (1 mmol), and solvent (2 mL).
[b] Isolated yields.

2.2. Preparation of $MgAl_2O_4$

$MgAl_2O_4$ was prepared according to co-precipitation method (Navaei Alvar et al., 2010) with modification. Typically, deionized water (100 mL) is added to a stoichiometric mixture of Mg $(NO_3)_2$s6H_2O (4.0 mmol, 1.024 g) and Al$(NO_3)_3$s9H_2O (4.0 mmol, 1.5 g) and sonicated for 30 min. Poly ethylene glycol (PEG) 2000 (2 g) is added as surfactant, and the pH of the slurry with continuous stirring is adjusted to 9 by dropwise addition of concentrated ammonia. After precipitation, the slurry is stirred magnetically for another 30 min and placed in ultrasound bath for 30 min. The mixture refluxed at 80 °C for 24 h under continuous stirring. Then the mixture was cooled to room temperature and centrifuged. The solid residue was dried at 100 °C for 24 h and calcined at 800 °C for 6 h.

2.3. General procedure for synthesis of 3-hydroxy 3-indolyl-indolin-2-ones

A mixture of indoles (1.0 mmol), isatins (1.0 mmol), and $MgAl_2O_4$ powder (0.2 mmol, 0.028 g) was stirred under solvent-free conditions at 60 °C. The progress of the reaction was monitored by TLC (eluent: *n*-hexan/EtOAc 2:1). After completion, methanol (10 mL) was added and the pure products were obtained by PLC method.

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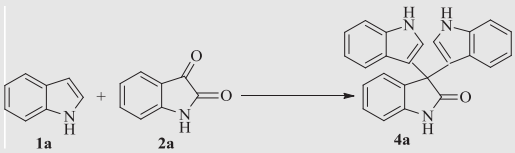
Table 2 $MgAl_2O_4$ catalyzed synthesis of 3-indolyl-3-hydroxy-indolin-2-one derivatives.[a]

Entry	R_1	R_2	R_3	R_4	Product	Time (min)	Yield (%)[b]	m.p. (°C)	Lit. m.p. (°C)
1	H	H	H	H	**3a**	20	82	295–298	293–295 (Rad-Moghadam et al., 2010)
2	H	H	$PhCH_2$	H	**3b**	65	87	121–123	120–124 (Shanthi et al., 2009)
3	H	H	H	NO_2	**3c**	15	92	186–187	187–189 (Rad-Moghadam et al., 2010)
6	H	Br	H	H	**3d**	70	78	310–312	314-316 (Shanthi et al., 2009)
4	Me	H	H	H	**3e**	55	94	184–185	181–183 (Rad-Moghadam et al., 2010)
5	Me	H	$PhCH_2$	H	**3f**	55	78	98–99	96–98 (Shanthi et al., 2009)
7			H	H	**3g**	70	82	165–166	163–166 (Li et al., 2014)

[a] Reaction conditions: indole (1 mmol), isatin (1 mmol), and $MgAl_2O_4$ (20 mol%) at 60 °C under solvent-free conditions.
[b] Isolated yields.

Table 3 Screening the condition of one-pot three-component condensation of indole (**1a**) and isatin (**2a**) under various conditions.[a]



Entry	Solvent	Temperature (°C)	Catalyst (mol%)	Time (min)	Yield (%)[b]
1	H_2O	r.t.	20	90	61
2	H_2O	Reflux	20	30	63
3	CH_3CN	r.t.	20	40	55
4	CH_3CN	Reflux	20	185	64
5	EtOH	r.t.	20	100	57
6	EtOH	Reflux	20	30	56
7	–	r.t.	20	65	60
8	–	60	20	35	80
9	–	80	20	25	82
10	–	100	20	25	83
11	–	80	30	15	84
12	–	80	35	15	84
13	–	80	–	180	21

[a] Reaction conditions: indole (2 mmol), isatin (1 mmol), and solvent (2 mL).
[b] Isolated yields.

2.4. General procedure for synthesis of symmetrical and unsymmetrical 3,3′-bis(indolyl)-indolin-2-ones

A mixture of indoles (2.0 mmol) (1.0 mmol of two different indoles for unsymmetrical correspondence), isatins (1.0 mmol), and $MgAl_2O_4$ (0.3 mmol, 0.037 g) was stirred under solvent-free condition, at 80 °C up to complete progression monitored by TLC (eluent: *n*-hexan/EtOAc 1:1). The pure products were obtained like Section 2.2 procedure.

2.5. General procedure for synthesis of 3,3′-bis(indolyl) methanes

A mixture of indoles (2.0 mmol), aldehydes (1.0 mmol), and $MgAl_2O_4$ (0.2 mmol, 0.028 g) was stirred at 100 °C under solvent-free condition up to complete progression monitored by TLC (eluent: *n*-hexan/EtOAc 4:1) and worked-up via Section 2.2 method to obtain the pure products.

2.6. 1-Benzyl-3-(1H-indol-3-yl)-3-(5-bromo-1H-indol-3-yl) indolin-2-one (5b)

m.p. 289–291 °C, IR (KBr) υ = 3400, 3260, 1690, 780 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 1.70–1.89 (m, 3H), 4.91–5.07 (dd, J = 15.6 Hz, J = 16.53 Hz, 2H), 6.51–6.55 (m, 1H), 6.75 (t, J = 7.7 Hz, 1H), 6.81–6.87 (m, 1H), 6.95–7.11 (m, 3H), 7.17–7.35 (m, 9H), 10.86 (d, 1H, NH), 10.97 (s, 1H, NH). Anal. Calcd. for $C_{31}H_{22}N_3OBr$: C 69.93, H 4.16, N 7.89%. Found: C 69.82, H 4.10, N 7.71%.

2.7. 5-Nitro-3-(1H-indol-3-yl)-3-(5-chloro-1H-indol-3-yl) indolin-2-one (5c)

m.p. 305–308 °C, IR (KBr) υ = 3424, 2923, 2855, 1647, 1512, 1460, 1028 cm^{-1}. ^1H NMR (DMSO-d_6) δ = 6.79–6.82 (m, 1H), 6.95 (m, 1H, NH), 6.97–7.03 (m, 1H), 7.11 (d, J = 2.29 Hz, 1H), 7.15–7.17 (m, 1H), 7.29–7.34 (m, 1H), 7.50 (t, J = 10.3 Hz, 2H), 8.01 (dd, J = 9.23, 2.67 Hz,1H), 8.21 (d, J = 2.38 Hz, 1H), 8.23 (d, J = 2.32 Hz, 1H), 8.47 (d, J = 2.65 Hz, 1H). Anal. Calcd. for $C_{24}H_{15}N_4O_3Cl$: C 65.09, H 3.41, N 12.65%. Found: C 65.02, H 3.59, N 12.21%.

2.8. 3-(1H-Indol-3-yl)-3-(2-methyl-1H-indol-3-yl)indolin-2-one (5d)

m.p. 310–311 °C. IR (KBr) υ = 3420, 1710, 1620, 1490, 1330, 1100, 741 cm^{-1}. ^1H NMR (DMSO-d_6) δ = 2.28 (s, 3H), 6.93 (s, 1H), 6.99–7.01 (m, 2H), 7.07 (t, J = 7.4 Hz, 1H), 7.21–7.24 (m, 2H), 7.30 (t, J = 7.1 Hz, 1H), 7.35–7.47 (m, 4H), 7.97 (t, J = 8.4 Hz, 2H), 8.0 (s, 1H, NH), 10.1 (br s, 1H, NH), 12.46 (br s, 1H, NH). Anal. Calcd. for $C_{25}H_{19}N_3O$: C 79.55, H 5.07, N 11.13%. Found: C 79.50, H 5.03, N 11.04%.

2.9. 1-Benzyl-3-(1H-indol-3-yl)-3-(2-methyl-1H-indol-3-yl) indolin-2-one (5e)

m.p. 262–264 °C, IR (KBr): ν = 3420, 3040, 1700, 1603, 1460, 740 cm^{-1}, ^1H NMR ($CDCl_3$): δ = 1.76 (s, 3H, Me), 4.98 (s, 2H, CH_2), 6.70 (t, J = 7.7 Hz, 1H), 7.11 (s, 2H), 6.85–6.86 (m, 3H), 6.95–6.98 (m, 3H), 7.26–7.38 (m, 9H), 11.10 (s, 1H, NH), 11.39 (s, 1H, NH). Anal. Calcd. for $C_{32}H_{25}N_3O$: C 82.20, H 5.39, N 8.97%. Found: C 81.95, H 5.03, N 8.04%.

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Table 4 $MgAl_2O_4$ catalyzed synthesis of symmetrical and unsymmetrical 3,3′-bis(indolyl)indolin-2-ones.[a]

Entry	R_1	R_2	R_3	R_4	R_5	Product	Time (min)	Yield[b] (%)	m.p. (°C)	Lit. m.p. (°C)
1	H	H	H	H	H	**4a**	15	84	313–315	312–314 (Alimohammadi et al., 2008)
2	H	H	H	H	Br	**4b**	55	71	312–314	308–310 (Alimohammadi et al., 2008)
3	H	H	H	H	NO_2	**4c**	135	77	300–301	297–298 (Alimohammadi et al., 2008)
4	H	H	H	H	Cl	**4d**	50	91	297–299	295–297 (Nikpassand et al., 2010)
5	H	H	H	Me	H	**4e**	130	82	291–294	291–293 (Alimohammadi et al., 2008)
6	H	H	H	$PhCH_2$	H	**4f**	70	84	262–264	288–289 (Alimohammadi et al., 2008)
7	Me	H	H	H	H	**4g**	55	83	298–299	211–213 (Alimohammadi et al., 2008)
8	Me	H	H	Me	H	**4h**	65	92	269–272	282–284 (Alimohammadi et al., 2008)
9	Me	H	H	$PhCH_2$	H	**4i**	85	73	209–211	211–213 (Alimohammadi et al., 2008)
10	H	H	Br	H	H	**4j**	55	93	303–305	300–302 (Haghighi and Nikoofar, 2014)
11	H	H	Br	H	Cl	**4k**	80	92	305–308	> 300 (Nikpassand et al., 2010)
12	H	H	OMe	H	H	**4l**	80	95	288–291	292–294 (Sharma and Sharma, 2010)
13	H	Me	H	H	H	**4m**	130	61	298–301	300–302 (Sarrafi et al., 2012)
14	H	Me	H	H	NO_2	**4n**	15	72	279–283	283–286 (Sarrafi et al., 2012)
15	H	H	Br	H	H	**5a**	85	91	284–285	284–286 (Rad-Moghadam et al., 2010)
16	H	H	Br	$PhCH_2$	H	**5b**	75	80	289–291	–
17	H	H	Cl	H	NO_2	**5c**	65	80	305–308	–
18	Me	H	H	H	H	**5d**	90	92	310–311	–
19	Me	H	H	$PhCH_2$	H	**5e**	115	84	262–264	–
20				H	H	**4o**	50	84	173–175	173–175 (Haghighi and Nikoofar, 2014)

[a] Reaction conditions: indole (2 mmol), isatin (1 mmol), and $MgAl_2O_4$ (30 mol%) under solvent-free conditions at 80 °C.
[b] Isolated yields.

3. Results and discussion

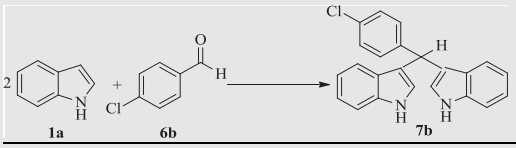
3.1. Characterization of catalyst

In the catalyst synthesis procedure the magnesium nitrate and aluminum nitrate solutions, as Mg^{2+} and Al^{3+} sources, were stirred together in the presence of PEG 2000 at pH = 9. The preparation equations can be proposed as follows (Scheme 2).

The shape and size uniformity of nanoparticles is a function of surfactant material. The surfactant also affected on clustering the nanoparticles. Nanocrystalline $MgAl_2O_4$ was characterized using different techniques. The SEM image has been illustrated in Fig. 1. It was confirmed that the catalyst was made up of particles with the average size of 40–50 nm with spherical morphology. Also the average crystallite size is estimated using Scherrer formula ($d = k\lambda/\beta\cos\theta$). The full width at half maximum (FWHM) is calculated for the main intense peak (3 1 1), λ is the wavelength of the X-ray (λ = 1.78 Å for Co anode), k is a constant between 0.89 and θ is the Bragg's diffraction angle. The β is sum of the β_{size}, β_{ins} and β_{strain}. The β_{strain} that identified the micro strain of crystal should be considered in size calculation. The instrumental broadening effect (β_{ins}) is reported by X-ray diffractometer that must be subtracted from β_{obs} which was measured by XRD instrument. Then the true value of β is calculated by $\beta_{size+strain} = \beta_{obs} - \beta_{ins}$. This value accounted is substituted in Scherrer formula. Then using this formula, the mean crystallite size is calculated 50 nm which corresponds to SEM image (Fig. 1). For this diffractometer β_{ins} is estimated as 0.0033 radians based on instrumental XRD pattern (see Fig. 3).

EDX in Fig. 2 shows that the catalyst mainly consisted of magnesium and aluminum. The weight percent of product confirms the molecular formula of $MgAl_2O_4$. Also, EDAX indicates that there are no impurities. The Au amount is negligible.

Table 5 Optimization of the reaction conditions in the synthesis of **7b**.[a]



1a 6b 7b

Entry	Solvent	Temperature (°C)	Catalyst (mol%)	Time (min)	Yield (%)[b]
1	H_2O	r.t.	20	350	–[c]
2	H_2O	Reflux	20	350	–[c]
3	CH_3CN	r.t.	20	350	–[c]
4	CH_3CN	Reflux	20	350	–[c]
5	EtOH	r.t.	20	350	–[c]
6	EtOH	Reflux	20	350	–[c]
7	–	r.t.	20	200	31
8	–	60	20	300	42
9	–	80	20	300	43
10	–	100	20	300	91
11	–	120	20	300	91
12	–	100	10	540	61
13	–	100	30	300	91

[a] Reaction conditions: indole (2 mmol), 4-chlorobenzaldehyde (1 mmol), and solvent (2 mL).
[b] Isolated yields.
[c] The substrate remained intact.

The morphology and phase identification of synthesized nanocatalyst were investigated using XRD pattern (Fig. 3) that was obtained for cobalt anode with the wavelength 1.7889 Å for Cu anode, and the 2θ must be multiplied by 0.86. The sharp peaks defined the crystal structure. According to Fig. 3, the peak values were observed at the following

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Table 6 $MgAl_2O_4$ catalyzed synthesis of bis(indolyl)methanes from indoles and aldehyde derivatives.[a]

Entry	R	Ar	Product	Time (h)	Yield (%)[b]	m.p. (°C)	Lit. m.p. (°C)
1	H	C_6H_5	**7a**	7.5	92	139–142	140–142 (Hojati et al., 2013)
2	H	4-ClC_6H_4	**7b**	5	91	74–77	74–76 (Hojati et al., 2013)
3	H	3-ClC_6H_4	**7c**	4	62	91–92	89–91 (Mohammadpoor-Baltork et al., 2006)
4	H	4-$MeOC_6H_4$	**7d**	9	56	187–189	180–182 (Hojati et al., 2013)
5	H	2-$MeOC_6H_4$	**7e**	4	64	135–138	133–135 (Yang et al., 2011)
6	H	4-$NO_2C_6H_4$	**7f**	2	54	214–218	218–220 (Hojati et al., 2013)
7	H	3-$NO_2C_6H_4$	**7g**	7	58	220–224	219–221 (Hojati et al., 2013)
8	H	2-$NO_2C_6H_4$	**7h**	9	63	209–211	210–212 (Yang et al., 2011)
9	H	3-BrC_6H_4	**7i**	2	87	187–190	189–191 (Tayebee et al., 2011)
10	H	2-OHC_6H_4	**7j**	5	78	107–109	103–104 (Yang et al., 2011)
11	H	Naphtyl	**7k**	11	98	227	220 (Mohammadpoor-Baltork et al., 2006)
12	H	4-OH-2-$MeOC_6H_3$	**7l**	10	45	124–127	126–127 (Hojati et al., 2013)
13	Me	4-ClC_6H_4	**7m**	1	66	241–243	236–238 (Pal, 2013)
14	Me	4-MeC_6H_4	**7n**	3	76	172–175	173–174 (Pal, 2013)

[a] Reaction conditions: indole (2 mmol), aldehydes (1 mmol), and $MgAl_2O_4$ (20 mol%) at 100 °C under solvent-free conditions.
[b] Isolated yields.

scattering angles 22.38, 36.85, 43.37, 53.07, 70.82 and 78.29 (that are reported using cobalt anode). These peaks correspond to 111, 220, 311, 400, 422, and 511 crystalline planes. The peaks show the $MgAl_2O_4$ nanocrystal with a spinel structure (according to JCPDS card No. 77-0435).

The FT-IR spectrum is shown in Fig. 4. The band at 624 cm^{-1} related to Al–O stretching vibration that corresponds to the AlO_6 groups that build up the $MgAl_2O_4$ spinel. The broad absorption at 3446 cm^{-1}, is the stretching vibration of hydroxyl (OH) and the peak at 1646 cm^{-1} due to the bending vibration of adsorbed water molecule. The major peaks at 700 with a shoulder at 818 cm^{-1} show the presence of Mg–O vibrations (Sundberg et al., 1992). The weak band at 1460 cm^{-1} provides the presence of organic residuals due to C–O stretching vibration of PEG 2000 in the calcined powder (Chandradass and Kim, 2010).

3.2. Catalytic activity of $MgAl_2O_4$ in the Synthesis of 3-hydroxy-3-indolyl-indolin-2-ones

To optimize the conditions, the one-pot reaction of indole (1 mmol) and isatin (1 mmol) in the presence of nanocrystalline $MgAl_2O_4$ was carried out under different conditions (Table 1). Examining different solvents confirms that solvent-free situation is the best choice (entries 1–7). Investigation of the temperature effect, corroborated that 60 °C is the best (entries 7–10). The catalyst amount has been also examined to obtain the satisfactory results that was 20 mol% of $MgAl_2O_4$ (Table 1, entries 9, 11–12).

On the basis of Table 1 results, the reaction of various indoles and isatins has been performed to prepare the corresponding 3-hydroxy-3-indolyl-indolin-2-ones within 15-70 min by 78–94% (Table 2). In order to explain the efficiency of catalyst pyrrole, another *N*-containing heterocycle reacted with isatin at its C-2 position successfully (Table 2, entry 7).

3.3. Catalytic activity of $MgAl_2O_4$ for the Synthesis of symmetrical and unsymmetrical 3,3-di(indolyl)indolin-2-ones

Here in, for optimizing, we have investigated the reaction indole (**1a**) (2 mmol) and isatin (**2a**) (1 mmol) in the presence of nanocrystalline $MgAl_2O_4$ (20 mol%) as a model reaction

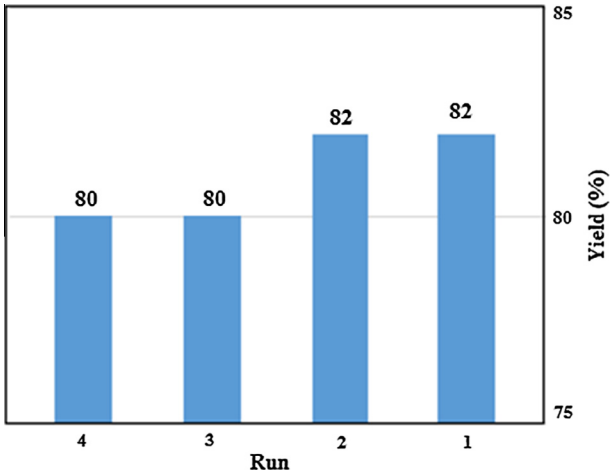

Figure 5 Reusability of $MgAl_2O_4$ for the synthesis of **3a**.

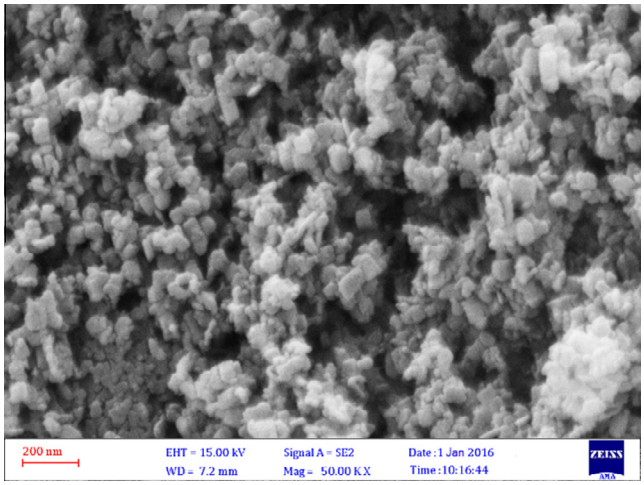

Figure 6 SEM image of the recovered nano-$MgAl_2O_4$ after four runs in the synthesis of **3a**.

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Table 7 Catalytic activity of nano-$MgAl_2O_4$ in comparison with other catalysts used for the preparation of **4a**.

Entry	Conditions	Time (h)	Yield (%)	Ref.
1	I_2 (10 mol%), CH_2Cl_2, r.t.	14	82	Subba Reddy et al. (2012)
2	Indium(III) acetylacetonate bonded silica gel ($In(acac)_3$-APSG, 10 mol%), H_2O/CH_3CN (4/1), r.t.	2.5	92	Sharma and Sharma (2010)
3	CAN (10 mol%), EtOH, ultrasound irradiation, r.t.	3	95	Wang and Ji (2006)
4	Prolinium triflate (ProTf, 10 mol%), CH_3CN, r.t.	5	90	Shiri (2013)
5	Boron trifluoride supported on nano-SiO_2 (nano-SiO_2-$BF_3^-CH_3OH_2^+$, 0.3 g), CH_3OH, reflux	0.33	95	Saffar-Teluri (2014)
6	Amberlyst-15 (0.3 g), H_2O, 70 °C	0.5	94	Sarrafi et al. (2012)
7	Nano-$MgAl_2O_4$ (30 mol%), solvent-free, 80 °C	0.25	84	This work

(Table 3). The condensation was carried out in various solvents and the results demonstrated that solvent-less media is the best choice (entries 1–7). Performing the temperature effect on the model reaction, affirmed that 80 °C heat could progress the condensation as well as possible (entries 7–10). In the next step the catalyst amount has been changed under solvent-free conditions at 80 °C (entries 11–12). The better results were obtained at 30 mol% loading. The model reaction has also been performed in the absence of catalyst that proceed smoothly in low yield (entry 13).

Eventually, on the basis of optimized conditions, the reaction of various indoles **1** with isatins **2** has been proceeded by $MgAl_2O_4$ (30 mol%) under solvent-free condition at 80 °C to obtain the symmetrical 3,3′-bis(indolyl)oxindoles (Table 4). As could be seen different indoles and isatins with electron-withdrawing and electron-donating substituents underwent the condensation at the C-3 position of indoles successfully (Table 4, entries 1–12). In order to check the expansibility of the nanocatalyst activity, the one-pot three-component condensation of 3-methylindole (**1e**) with isatins has also been performed. The results confirmed that the condensation occurred at the C-2 position of **1e**, in which the more active C-3 position is blocked, to afford the corresponding 3,3′-bis(3-methyl-2-indolyl)indolin-2-ones (entries 13–14). Another interesting aspect of oxindole synthesis is preparing unsymmetrical 3,3′-di(indolyl)indolin-2-ones. For this reason the one-step three-component condensation of isatins (1 mmol) with two different indoles (each of them 1 mmol) has been surveyed in the presence of 30 mol% of $MgAl_2O_4$ at 80 °C under solvent-free conditions (entries 15–19). The obtained results determined the high catalytic activity of our nanocatalyst, as no by-products of symmetrical oxindoles have been observed. It must be mentioned that in our literature review, one-step condensations for preparation of unsymmetrical oxindoles analogues from indoles and isatins are rare. Extension success of $MgAl_2O_4$ validates in the condensation of pyrrole with isatin (Table 4, entry 20) yielded to 3,3′-bis(2-pyrrolyl)indolin-2-one.

3.4. Catalytic activity of $MgAl_2O_4$ synthesis of bis(indolyl) methanes

Sequentially, in order to handle the catalyst proficiency, one-pot pseudo three-component reaction of indole (2 mmol) and 4-chlorobenzaldehyde (1 mmol) has been selected as the model reaction. Various reaction conditions have been tested. The results are summarized in Table 5. Screening the solvent effect showed that the reaction did not proceed in solvent and the best result is solventless media (entries 1–7). Increasing the temperature up to 100 °C, enhanced the reaction yield (entries 7–11). The catalyst amount was also investigated and the best load was 20 mol% (entries 10, 12–13).

Perpending the optimized conditions the reaction of indoles with various aldehydes has been done. The results are shown in Table 6. Benzaldehyde and its electron-donating and withdrawing analogues carried out the reaction successfully. 1-Naphthaldehyde has also done the process well. Different aromatic ketones such as acetophenone and its 4-nitro- and 4-methoxy derivatives did not perform the reaction. Cyclohexanone, as an aliphatic ketone, also failed to condense with indole. We have also checked butanal and crotonaldehyde, as aliphatic and allylic aldehydes respectively, also did not vanquish the reaction. These data affirmed that $MgAl_2O_4$ is a chemoselective catalyst to prepare bis(indolyl)methanes, as only aromatic aldehydes could undergo condensation with indoles.

3.5. Catalyst stability and recycling

The reusability of nanocrystalline $MgAl_2O_4$ for the MCR to afford **3a** was also investigated for four runs. After reaction completion, the mixture was diluted with hot ethanol. The catalyst was separated by filtration, washed with hot ethanol, and air-dried and used directly without a considerable loss of catalytic activity (Fig. 5). In the final cycle of the examination, the recovered nano-$MgAl_2O_4$ characterized by the SEM image is shown in Fig. 6.

In the final part, our procedure has been compared by other reported procedures in the literature for the preparation of **4a**. The results at Table 7, confirmed the activity of the modified nanocrystals of $MgAl_2O_4$ in the mentioned MCRs.

4. Conclusion

In conclusion, nanocrystalline $MgAl_2O_4$ was obtained by a simple, modified, and useful co-precipitated method and characterized in terms of its structural aspects. This catalyst is very active in the preparation of 3-hydroxy-3-indolyl-indolin-2-ones, 3,3′-bis(indolyl)indolin-2-ones, and 3,3′-bis(indolyl)methanes under solvent-free conditions. Various isatins and indoles reacted with each other in different conditions. The catalyst can be recovered and reused within 4 runs without losing activity which makes this protocol economic, benign, and a waste-free chemical process.

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